Implementing Federal Guidelines for Human Research: A Researcher's Perspective

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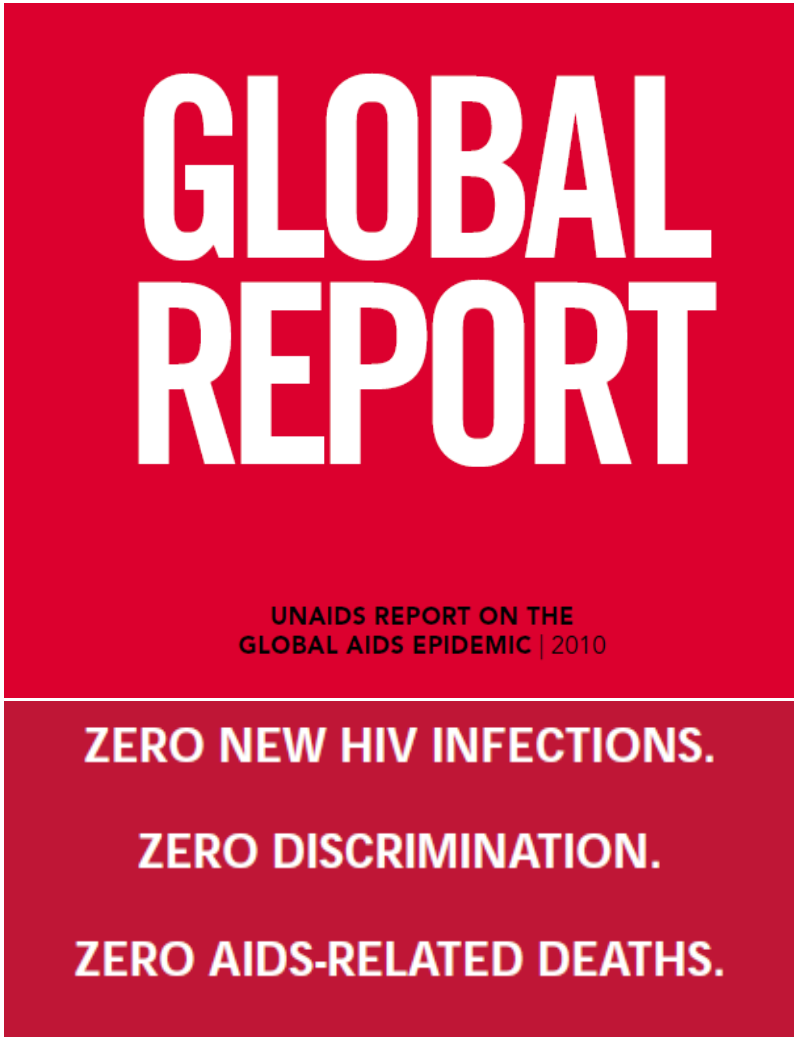
HIV in 2011

- Declining HIV incidence in many African countries compared to 2007
- We may be at or nearing the 'tipping point'
  - If we increase coverage of HIV testing, treatment, and other effective HIV prevention strategies
- Research has contributed to this decline, and can continue to be part of the public health response



Antiretrovirals for prevention

PrEP in HIV-uninfected persons:

- A gel or pill decreases HIV acquisition by **39%-42%** in young South African women and MSM

ART for HIV-infected persons:

- Early ART in HIV+ persons decreases HIV transmission by **96%**

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The New York Times

Africa

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African Studies Give Women Hope in H.I.V. Fight

Joao Silva for The New York Times

Volunteers who participated in a study on reducing the risk of HIV infection in women listened as the test results were announced during a meeting in Vulindlela, Kwazulu-Natal, South Africa.

By CELIA W. DUGGER
Published: July 19, 2010

VULINDLELA, South Africa — With an AIDS vaccine still out of

RECOMMEND

"I'm afraid you've had a paradigm shift."

A preview of my conclusions

- International clinical research can and is being implemented to the highest ethical standards
- Substantial effort is required & there are multiple challenges & barriers to achieving this
  - Multiple layers of review; sometimes inconsistent recommendations
  - Conservative approach (medical vs public health perspective) leads to substantial delays
  - Collaborative, capacity-building research is essential
- Given high HIV incidence among women in sub-Saharan Africa, there is an urgent need to reevaluate barriers to including pregnant & breastfeeding HIV-women in research

Introduction to perspectives: My research experience

1989-94 – Epidemiology of Sexually transmitted infections among men who have sex with men (MSM) in US & Peru

1995-03 – HIV vaccine preparedness cohorts, phase II & III HIV vaccine trials, & behavioral intervention in MSM in US

2002-08 – **Phase III trial of suppression of genital herpes to prevent HIV acquisition: 3265 MSM in US, Peru & women in Africa (9 sites; NIH funded)**

2003-09 – **Phase III trial of suppression of genital herpes to prevent HIV transmission: 3408 heterosexual HIV serodiscordant couples in 14 sites in East & southern Africa (sponsor: BMGF)**

2007-present – Phase III trial of antiretroviral pre-exposure prophylaxis (PrEP): 4758 heterosexual HIV serodiscordant couples in Kenya & Uganda (sponsor: BMGF)

2007-present – Executive Committee, Microbicides Trial Network (MTN, NIH)

2008-2012 – Pilots of combination HIV prevention (home-based HIV testing, linkages to ART & prevention (Uganda & South Africa, NIAID funded)

– Pending proposal for community RCT in KwaZulu-Natal, So Africa

Principles & realities of international HIV prevention & vaccine research

- Test interventions that can be delivered, if effective
- Poverty levels, stigma, & access to quality health care
  - Research in 'vulnerable populations'
- Understanding of consent by individuals with low literacy
- Multiple, sometimes inconsistent reviews: funder, US and international IRBs
- Insurance coverage
- Use of stored samples, esp for genetic studies
- Evolving standards of care: interpretations & expectations
  - Examples of male circumcision & earlier ART initiation
- Researchers obligations for providing services
  - Example of ART for HIV seroconverters during trial
- Post-trial access for effective interventions

HSV-2 Suppression to Prevent HIV Transmission: Partners in Prevention

3408 HIV- discordant couples with HIV+ partner also HSV 2-coinfected

↓

Randomize HIV/HSV-2 + persons not eligible for ART by national guidelines (CD4 ≥250)

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Acyclovir 400 mg twice daily

Placebo twice daily

↓

Follow couples for 1-2 years

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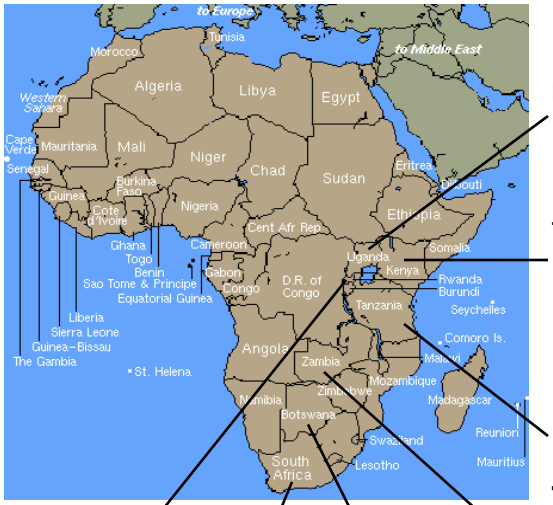
Primary endpoint: HIV infection in HIV-negative partner



Kampala, **Uganda**

Nairobi, Thika, Eldoret, Kisumu, **Kenya**

Moshi, **Tanzania**

Lusaka, Kitwe, Ndola, **Zambia**

Gaborone, **Botswana**

Kigali, **Rwanda**

Johannesburg (Soweto, Orange Farm), Cape Town (Gugulethu), **South Africa**

Summary of Partners in Prevention HSV/HIV Transmission Study

- ~55,000 couples of unknown status HIV tested & pre-screened across 14 sites in East & southern Africa
- 6,543 HIV discordant couples screened
- 3,408 HIV discordant couples enrolled (3,007 ineligible)
- High retention at 24 months (92% HIV+ & 84% HIV- partners)
- High drug coverage (85%)

Partners in Prevention HSV/HIV Transmission Study
Community Outreach and Recruitment

Partners in Prevention HSV-HIV Trial: What it Took

- 1½ yrs to build a Coordinating Center at an academic center; prepare 14 sites, 7 of which were new to clinical trials
- 20 IRB reviews of initial protocol and protocol revision
- Translation & back-translation into 16 languages:
  - 6 ICFs (3 for HIV+, 3 for HIV- partner)
  - 304 case-report forms (CRFs) into 16 languages
- 579,000 CRFs faxed to Seattle; 617 QC reports (20,500 pgs)
- 2 million samples collected
  - ~750,000 specimens shipped to Seattle Central Repository
  - For HSV & HIV confirmation, HIV viral load, HIV sequencing of endpoints
- 100s of quarterly monitoring & site visits, & conference calls

Lesson Learned: HIV discordant couples are key

- A high proportion of new HIV cases in Africa occur in cohabitating HIV discordant couples (= in which one partner is HIV infected and the other is HIV uninfected)
- In a couple in which one member is HIV+, there is only a 50:50 chance that the other will be HIV+
- ~30% of HIV infections within serodiscordant couples come from an outside partner
- Even with intensive risk reduction counseling, HIV risk is high for HIV-uninfected partners in discordant couples, particularly in couples desiring children

Ongoing PrEP efficacy studies

Location	Sponsor/ Funder	Population	N	PrEP Agent	Status
Thailand *Bangkok Tenofovir Study*	CDC	IDU	2400	TDF	Fully enrolled Results 2012
Kenya, Uganda *Partners PrEP Study*	UW / BMGF	HIV discordant couples	4758	TDF, FTC/TDF	Fully enrolled Results 2012
South Africa, Uganda, Zimbabwe *VOICE / MTN 003*	MTN / NIH	Women	5000	TDF, FTC/TDF, Vaginal tenofovir gel (daily)	93% enrolled Results 2013

- Safety, efficacy, resistance & costs will inform choice of drugs for PrEP roll-out
- Full spectrum of safety & efficacy will not be known among
  - *Pregnant and breastfeeding women*
  - *Adolescents (highest HIV incidence in young African women)*

Partners PrEP Study design

4758 HIV discordant couples
(HIV+ partner does not yet qualify for ART)

↓

Randomize HIV- partners
(normal liver, renal, hematologic function; not pregnant/breastfeeding)

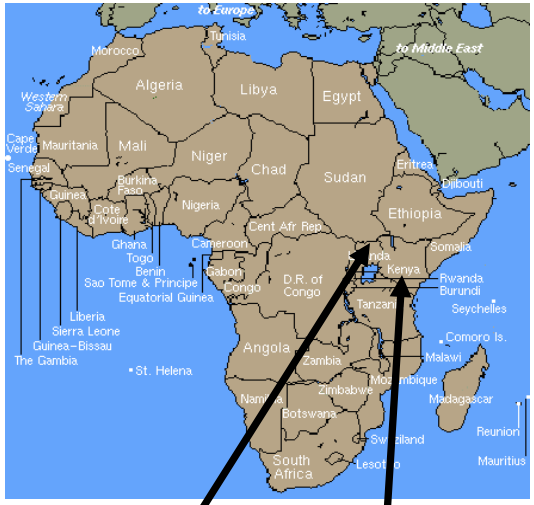
↙ ↓ ↘

TDF once daily | FTC/TDF once daily | Placebo once daily

All receiving HIV ↓ **prevention services**

Follow couples for 24-36 months

1° endpoint: HIV infection in HIV-negative partner
Co- 1° endpoint: Safety



Jinja, Kabwohe, Kampala, Mbale, Tororo, **Uganda**

Eldoret, Kisumu, Nairobi, Thika, **Kenya**

PARTNERS PrEP STUDY

International, collaborative research can be high quality & truly capacity building

- Human subjects, clinical (GCP) & laboratory (GCLP) training
- Monitoring visits every 6 weeks
- Durable capacity building
  - Mentoring young investigators
  - Clinical & laboratory infrastructure
  - Couples counseling programs

Dr. Nelly Mugo, Univ of Nairobi

Couples counseling: Mbale, Uganda

4 of 9 Partners PrEP sites were new to clinical research …

Tororo site renovation: February to Nov 2008

Eldoret data room

Nairobi pharmacy

Imperative for finding new biomedical HIV prevention strategies for pregnant women

- Risk of HIV acquisition is high for women during pregnancy
- Risk of perinatal HIV transmission is high during acute HIV infection
- Pregnant & breastfeeding women are one of largest under-represented populations in HIV prevention research
- Generalizability concerns if pregnant & breastfeeding women are excluded from studies
- Ensures a delay in obtaining critical safety data
- Relegates pregnant women & providers to either choosing new interventions without sufficient safety data
- Lack of harmonization between federal agencies with review authority

Relevance of studying biomedical HIV prevention strategies in pregnant & breast feeding women

- ~60% of HIV infections in subSaharan Africa are in women
- During pregnancy, women have high risk of HIV acquisition
  - 13% in recent study in western Kenya
- Partners in Prevention HIV/HSV Transmission Study
  - 2-fold increased HIV acquisition in HIV-negative pregnant women
  - 2-fold increased HIV transmission from pregnant HIV-infected women to their HIV-negative male partners

Issues to consider for prevention research in HIV-negative pregnant women

- What constitutes minimal risk?
- Is evidence of efficacy in non-pregnant adults (e.g. FDA approval) required before a drug is studied in pregnant women?
- If so, how will safety data in pregnancy be acquired once a product is approved and used widely in the population?
- Balance caution with need to proactively obtain safety data for products which, if shown effective in other populations, will be used without safety data by:
  - *Non-contracepting young women at high risk of pregnancy & HIV*
  - *Pregnant women at high risk for HIV*

Barriers to Enrolling HIV-infected Pregnant Women in Clinical Research

- 45 CFR 46.204e requires paternal and maternal consent for enrollment of pregnant women
  - When intervention is of potential benefit to fetus but not the mother
- Paternal consent for enrollment of HIV-infected pregnant women into trials requires disclosure of maternal HIV status
- Partner notification is encouraged, must be done carefully, & and is not always possible immediately
  - Thus, may hinder enrollment of HIV-infected pregnant women
- Regulation changed in end of Clinton administration but then overturned with change of administration
- Recommend re-evaluation of ethical issues regarding paternal consent for enrollment of pregnant women into trials

Summary of my conclusions

- International clinical research can and is being implemented to the highest ethical standards
- Substantial effort is required & there are multiple challenges & barriers to achieving this
  - Efficient, coordinated IRB reviews for multi-center studies
  - Feasibility of joint or external IRB review for int'l research
  - Needs assessment of international IRBs
  - Collaborative, capacity-building research is essential
- Evaluate barriers to including pregnant & breastfeeding HIV- women in research
  - Harmonization of federal agencies involved in review

International clinical means overcoming challenges

"**Motto: Endeavour to Excel**"
Kisumu, Kenya January 2009

Thank you to my many partners on the road long-travelled for HIV-1 prevention

If you want to go fast, go alone.

If you want to go far, go together.

– African proverb

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